REMARKS

Reconsideration and allowance are respectfully requested. Claims 10 to 16 are pending and are at issue. It is respectfully requested that the present amendments after a final rejection be entered, as the amendments either put the case in condition for allowance or put it in better form for appeal.

The amendments to the specification are made to correct formal matters, raised by the Examiner, concerning trademarks. The amendments add no new matter and raise no new issues for consideration by the Examiner.

Similarly, the amendments to the claims also add no new matter and raise no new issues for consideration by the Examiner, as the prior art discussed has all previously been cited and considered by the Examiner.

Substance of the Interview

Applicants thank the Examiner for granting a telephonic interview to applicants' representative. The rejections made in the final Office Action of July 1, 2008 were discussed, in particular the Section 101 and Section 112 rejections made based on the format of the claims. It is believed that the present amendments to the claims obviate those rejections.

Objection to the Specification

The specification was objected to based on the inclusion of some trademarks without indicating their nature. The specification has been reviewed and amended and it is believed that in those instances where trademarks are mentioned, the specification indicates the nature of the trademark by capitalization and a generic description. It is thus respectfully submitted that the ground for the objection to the specification has been overcome, and should be withdrawn.

The Rejections Under 35 U.S.C. §§ 101 and 112

Claims 10 to 16 were rejected for not being patentable subject matter, for being indefinite, and for lack of enablement. The rejection was based on the recitation of SEQ

ID NO:2 in the claims without an antecedent "an IGFBP-4 polypeptide consisting of" clause. Present claims 10 to 16 now include this clause. The amendment of the claims to include this clause raises no issues of new matter. In light of the amendments to the claims, it is respectfully submitted that the grounds for rejection of claims 10 to 16 under 35 U.S.C. §§ 101 and 112 have been overcome, and the rejections should be withdrawn.

The Rejections Under 35 U.S.C. § 103(a)

Should it be the Examiner's position that the grounds for the obviousness rejections of the claims set forth in the Office Action of August 9, 2007 remain applicable to present claims 10 to 16, it is respectfully requested that the following arguments be considered.

In particular, with respect to claims 10 and 14 to 16 and the disclosure of WO1994/22466 ("Cox") in view of Bethel, applicants request consideration of the following comments.

The Examiner has cited Cox for its disclosure of pegylated IGFBP-1, and Bethel for the sequence of IGFBP-4. The Examiner also apparently attributed to Cox the teaching that "...PEGylation of IGFBPs was know to increase the serum half-life of the polypeptides, while retaining their activity..." This last statement is unsupported by Cox. At page 12, lines 6 to 20 of Cox, it is disclosed that in order to link PEG to IGFBP-1, one should create a mutant molecule that contains cysteines in non-wild type positions, in order to reduce the possibility that the PEG molecules will bind to cysteines that are involved in receptor binding or IGF binding. Thus, Cox teaches that in order to maintain activity with a pegylated IGFBP-1, you need to mutate it, i.e., that an unmutated IGFBP pegylated at a native cysteine will lose activity, be it receptor binding or IGFBP binding.

Thus, from the teaching of Cox and Bethel, alone or in combination, it cannot be concluded that a pegylation of SEQ ID NO:2, as presently claimed, would result in a biologically active molecule, and one of ordinary skill in the art would have actually concluded, based on the disclosure of Cox, that one would have needed to modify the

sequence of SEQ ID NO:2 to add non-wild type cysteines in order to get a pegylated, active molecule.

Further, even if the cited prior art provided any basis for concluding that there was a reasonable expectation that one could pegylate one or more wild-type cysteines of SEQ ID NO:2 and retain activity, there are 20 cysteines in SEQ ID NO:2 that could potentially be modified, and the cited art clearly is devoid of any guidance as to which of these could be modified without losing activity. There is also no hint in any of the cited that the modification of SEQ ID NO:2 at cysteines 110 and/or 117 would provide a pegylated protein with the improved properties recited in the present specification, e.g., see page 4, lines 3 to 10.

Because claims 10 and 14 to 16 cannot properly be said to be obvious over the combined disclosures of Cox and Bethel, claims 11 to 13, dependent on claim 10, also cannot be said to be obvious over the combined disclosures of Cox, Bethel, and Veronse.

The Examiner had rejected claims 10 and 14 to 16 over the disclosures of U.S. Patent 6,004,775 ("Shimasaki") in view of U.S. Patent 6,207,640 ("Attie") and Francis et al. ("Francis"). Applicants request reconsideration of the following comments.

Shimasaki was cited for the disclosure of the amino acid sequence of IGFBP-4, and that such peptides are useful as components of antineoplastic compositions. The Examiner acknowledged that Shimasaki is silent with respect to pegylation of IGFBP-4. Attie was cited for the disclosure of pegylation of IGF-I or growth hormone to improve the circulating half life of these proteins. Francis was cited for a general disclosure about the advantages that can be provided by pegylation of therapeutic proteins. The Examiner asserted that the combined teachings of these references would have provided reasons to one of ordinary skill in the art to make the presently claimed conjugates, with a reasonable expectation of success.

Applicants previously pointed to Cox, above, and the Examiner's comments with respect to enablement as proof that one of ordinary skill in the art would have had no reasonable expectation of success that modifying any of the cysteines of SEQ ID NO:2 would have yielded an active conjugate. As noted above, Cox teaches that one needs

to provide non-native cysteines if one wants to conjugate IGFBP-1 with polyethylene glycol and retain activity. The Examiner, in the August 8, 2007 Office Action, provided a discourse on the unpredictability that modifications to protein structures can have on activity. Clearly, then, one of ordinary skill in the art would have no idea what effect modification of any of the 20 particular cysteines of SEQ ID NO:2 would have on the activity, and based on Cox would avoid such modifications and only modify on non-native, mutant cysteines. None of Shimasaki, Attie, or Francis provides any guidance as to which, if any, of the native cysteines of SEQ ID NO:2 can be pegylated while retaining activity, much less why one would choose the specific cysteines 110 and 117 recited in the present claims. Thus, it is respectfully submitted that the cited combination of prior art (Shimasaki, Attie, Francis) cannot properly be said to render the present claims obvious.

Because the combination of Shimasaki, Attie, and Francis do not render claim 10 obvious, the combination of Shimasaki, Attie, Francis, and Veronse cannot render dependent claims 11 to 13 obvious.

In light of the above remarks and amendments, it is respectfully submitted that all of claims 10 to 16 are free of the prior art, and are in condition for allowance.

No further fee is required in connection the filing of this Amendment. If any additional fees are deemed necessary, authorization is given to charge the amount of any such fee to Deposit Account No. 08-2525.

Respectfully submitted,

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